Results

- Increased investment in facilities
- More emphasis on controlling process
- Significant increase in communication between industry and agency
- Improved consistency
- Comprehensive feedback to industry

Where Are We Now?

- Sixth anniversary
- Harmonization with CDER and CDRH
  - Stability Requirements for Licensed In Vitro Diagnostic Products (Compliance Policy Guide)
  - Guide to Inspections of Viral Clearance Processes for Plasma Derivatives
  - Revision to Requirements for Licensed Anti-Human Globulin and Blood Grouping Reagents – Direct Final Rule

Where Are We Now?
continued

- Ongoing efforts focused on
  - Consistency
  - Inspection timeframes

What's Next for Team Biologics?

- We are in the midst of an evaluation – build on and improve process
  - Adopt internal quality management system
  - Develop metrics to determine impact on industry
  - Standardize training and qualifications of Core Team members
  - Risk-based work planning
  - Increased communications between headquarters and field

What's Next for Team Biologics?
continued

- Some changes are likely
  - Nature of oversight of Core Team
  - Role of product specialists
  - Measuring success
- Related activity impacting change
  - Pharmaceutical CGMPs For The 21st Century

Relationship of Team Biologics to CGMP Initiative

- Science based
- Dispute resolution
- “Improve operations of Team Biologics”
  - Immediate goal
- “Evaluate the feasibility of establishing dedicated cadres of pharmaceutical inspectors”
  - Intermediate goal

Additional Overlapping Areas
Team Biologics – CGMP Initiative

- Measuring success
- Quality definition
- Training of investigators
- Consistency of application of regulations
- Center review of proposed Warning Letters
  - In addition to current Office of Chief Counsel review
  - Similar to CBER existing practice

Team Biologics

Conclusions

- Team Biologics continues to evolve
- CGMP Initiative should have positive impact on efforts
- Industry can play active role
  - e.g., dispute resolution

Pre-Approval Inspections

- Manufacturing deficiencies continue to hinder speedy approvals
- Some issues observed more often than others
- Greater attention to these issues could prevent delays

Pre-Approval Inspection Issues

- Quality Agreements (contract manufacturers)
  - Report deviations not directly related to product manufacture?
  - Example: Failure in bracketing manufacture not reported to allow impact assessment of product

Pre-Approval Inspection Issues
continued

- Quality Agreements (continued)
  - Does change control system include notification of applicant and/or direct involvement of applicant in implementation decision?
  - Example: Does introduction of an investigational product require applicant notification?

Pre-Approval Inspection Issues
continued

- Process Validation/Manufacturing Consistency
  - Performed and completed prior to inspection?
  - Demonstrated consistency in manufacturing
- Equipment and Systems Qualifications
  - Not done at all
  - In-progress
  - Did not include critical parameters

Pre-Approval Inspection Issues
continued

- Quality Control Oversight
  - Investigations of deviations
  - Corrective and preventative actions
- Standard Operating Procedures
  - Not capturing actual practice
  - Lack of SOP

CBER Compliance Activities

- Compliance Actions and Data
- Examples of Warning Letter Citations FY01-03

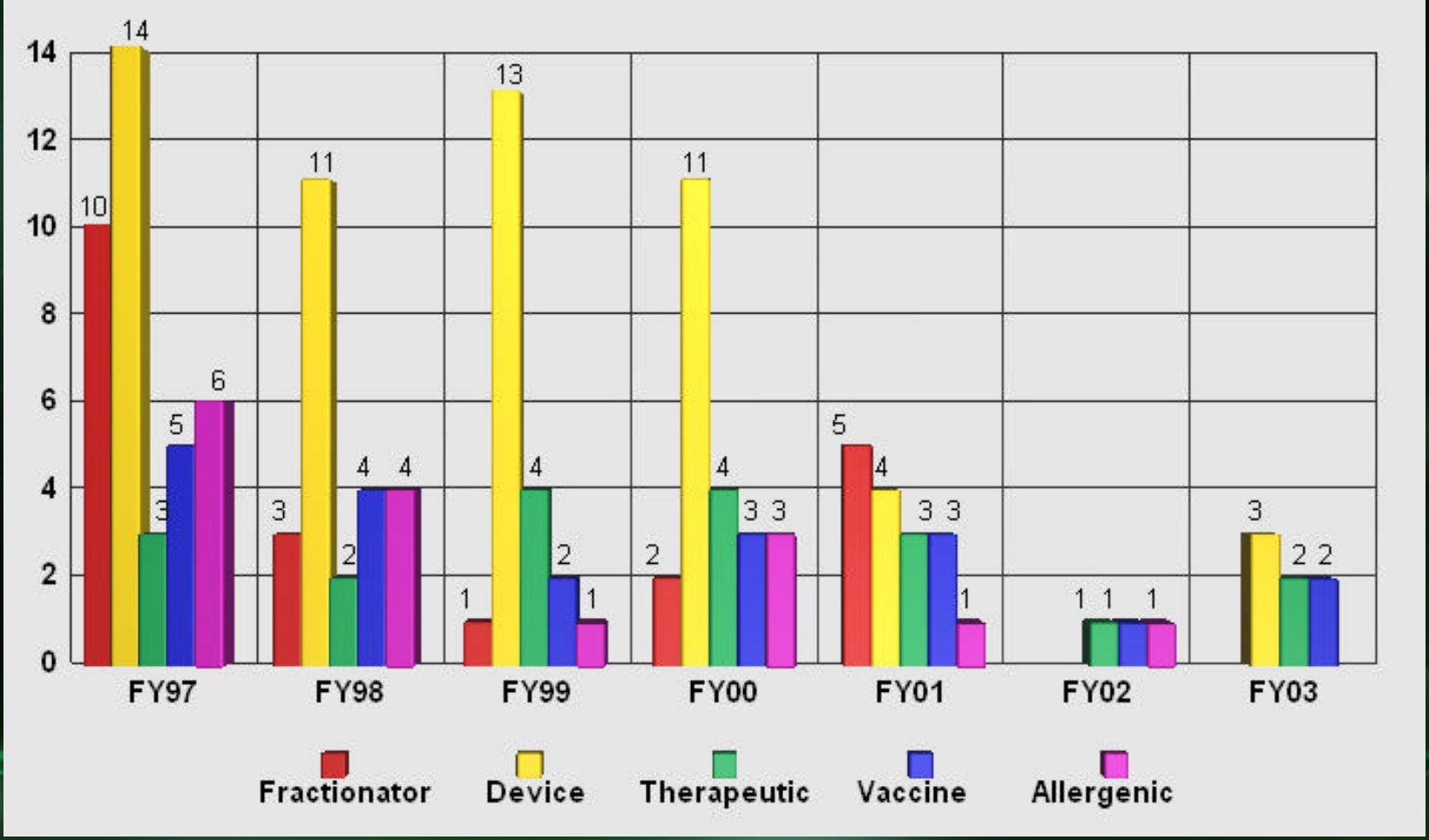
Compliance Actions

- Warning Letter
- License Suspension
- Notice of Intent to Revoke
- License Revocation
- Seizure
- Injunction
- Recall

Warning Letters

- Deviations determined to be so significant as to warrant potential enforcement action
- Notification to manufacturer
- Prompt correction

Warning Letters



License Suspension

- 21 CFR 601.6
- Grounds for revocation exist
- Danger to health
- Prohibits interstate distribution
- Requires notice to selling agents and distributors
- Records of same to CBER

License Suspension
continued

- Proceed to revocation, or possibility of resolution
- May be company-wide or site specific

License Revocation

- 21 CFR 601.5
- May be initiated by manufacturer or by FDA
- Discontinuation of manufacturing
  - Manufacturer request for revocation
  - Revocation initiated by FDA
- Unable to gain access to establishment or location

License Revocation
continued

- Failure to report manufacturing change
- CGMP deficiencies
- New method of manufacturing
- Product not safe and effective for intended use(s)/misbranded
- May request hearing

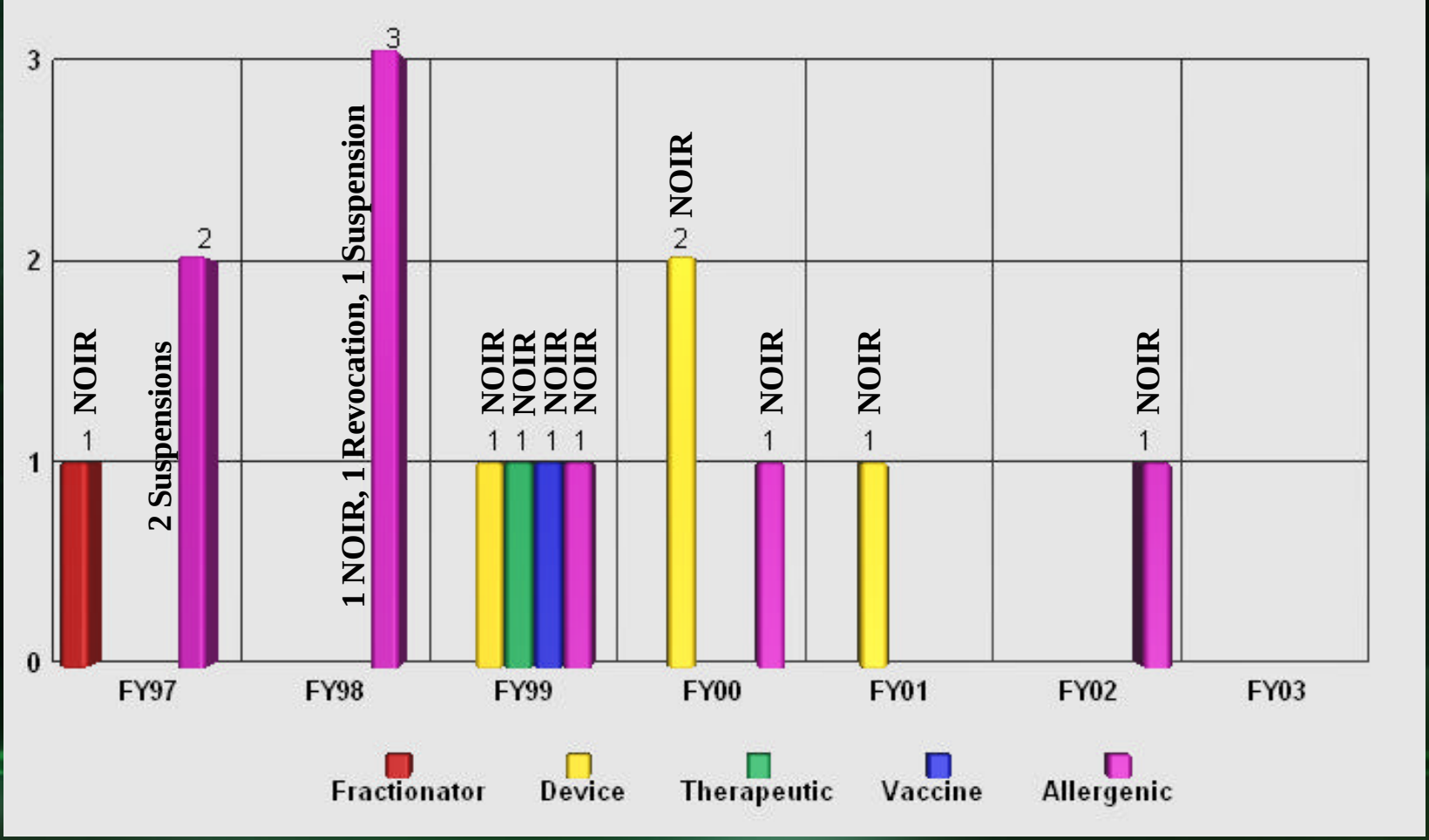
Types of Revocation

- Notice of Intent to Revoke
  - Continuing, significant deficiencies
  - Prior warnings
  - Opportunity to correct and achieve compliance (“reasonable period”)
  - If compliance not demonstrated, notice of opportunity for hearing (unless waived)

Types of Revocation
continued

- Direct Revocation
  - In cases involving willfulness, FDA will proceed directly to revocation
  - No further opportunity to demonstrate compliance

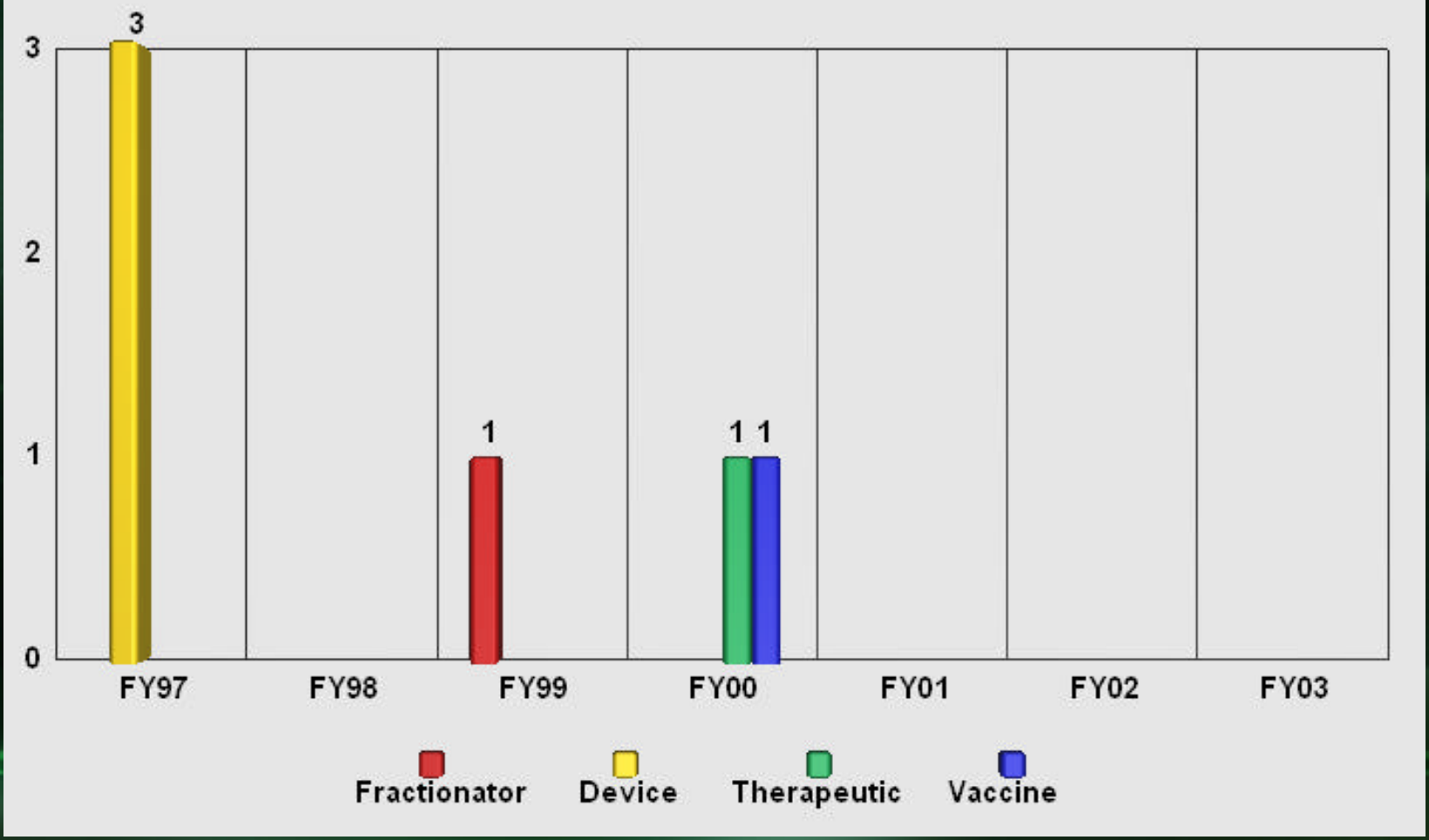
License Suspension, Revocation, and Notice of Intent to Revoke



Other Actions

- Injunction – Issued by Court
  - To stop or prevent actions that lead to violation of law
  - To correct the conditions that caused the violation to occur
- Seizure – Issued by Court
  - Removes product from market
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) – clinical investigators
  - Relates to CBER oversight of clinical investigations

Seizures


3
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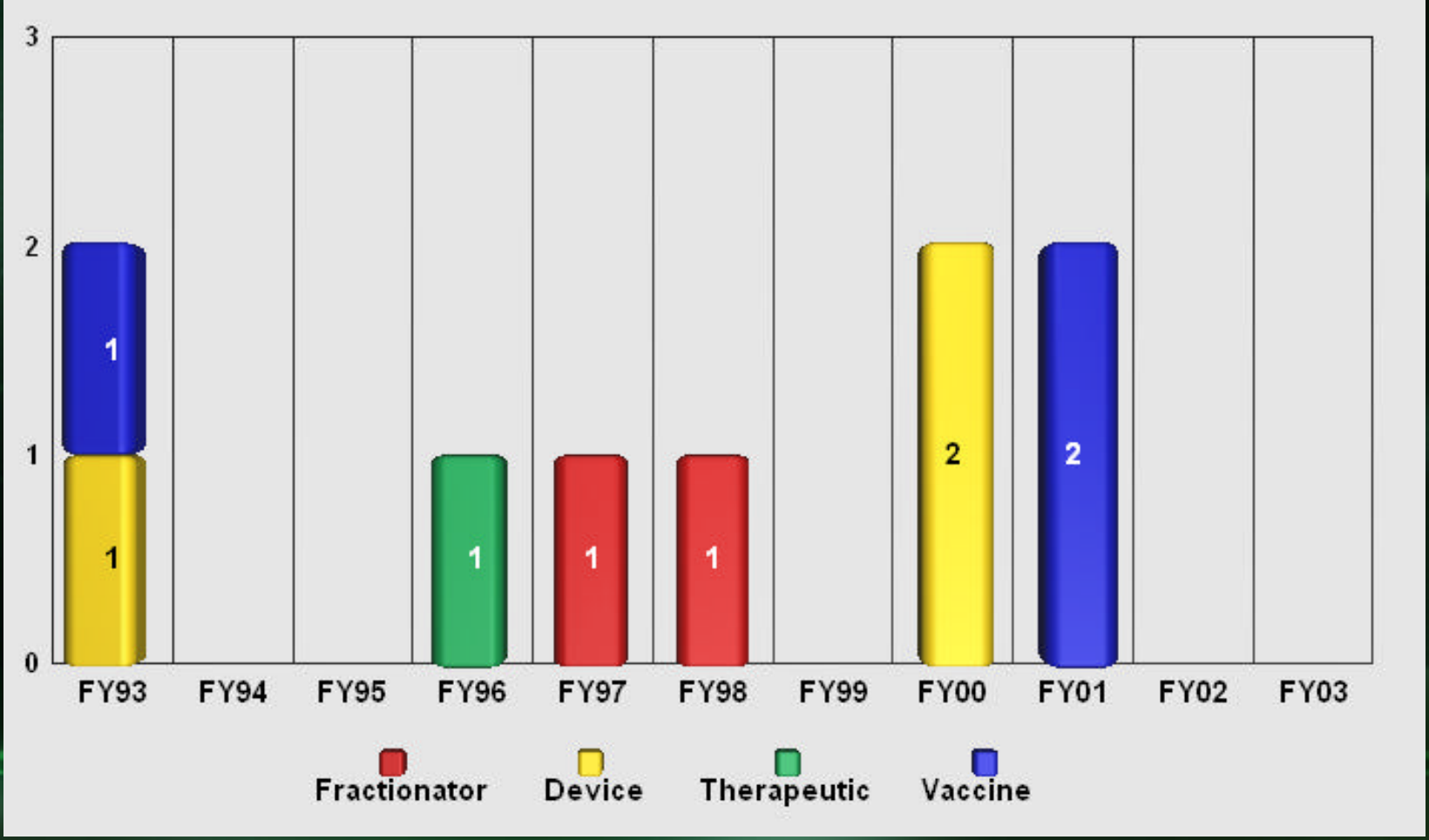
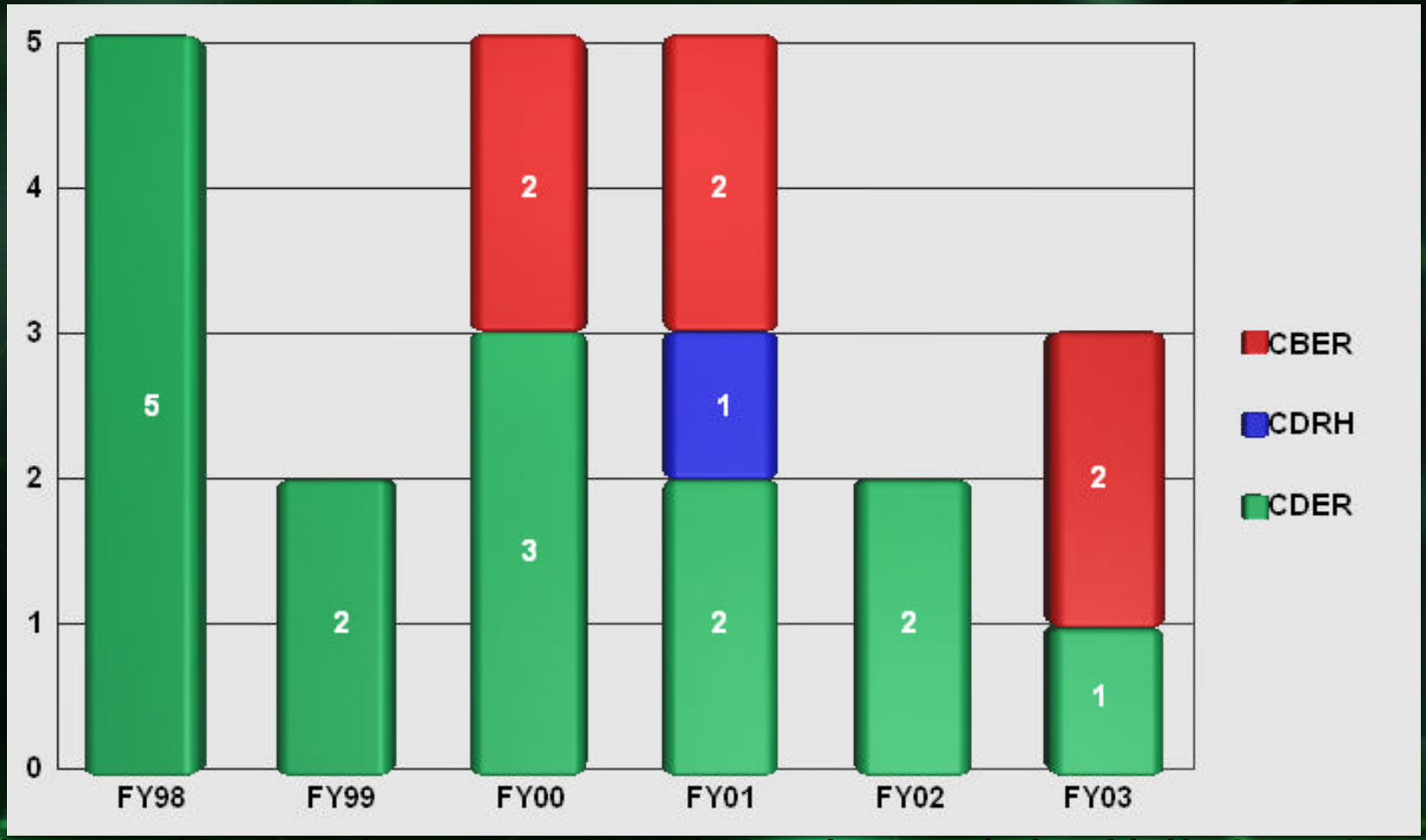
FY97
FY98
FY99
FY00
FY01
FY02
FY03
Fractionator
Device
Therapeutic
Vaccine

Injunctions



NIDPOE Letters

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain



To date, Notice of Opportunity for Hearing issued for 5 of 6 CBER letters – 1 of 4 disqualified by Consent Agreement

* As of October 16, 2003

Recalls

- 21 CFR Part 7 Subpart C
  - "Recalls (Including Product Corrections) – Guidance on Policy, Procedures, and Industry Responsibilities"
- Voluntary action in lieu of FDA-initiated court action for product removal or correction
- Voluntary action to carry out firm's responsibility to protect the public health with respect to its products

Recall Classifications

- Class I
  - Reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death
- Class II
  - Use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
- Class III
  - Use of, or exposure to, a violative product is not likely to cause adverse health consequences